REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-20 are pending. Claims 9-10 and 17-18 were withdrawn from consideration by the Examiner as directed to nonelected subject matter. Their rejoinder is requested upon an indication that the elected product claims are allowable. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry.

Specification/Claim Objections

The specification was objected to. Its amendment as suggested by the Examiner moots this objection. The first occurrence of oxaloacetate hydrolase is already accompanied by its abbreviation OAH at page 2, line 5, of the specification. The first occurrence of microtiterplate is accompanied by its abbreviation, which is inserted at page 7, line 29, of the specification.

Claim 5 was objected to. Its amendment as suggested by the Examiner moots this objection.

Withdrawal of the objections is requested.

35 U.S.C. 112 – Definiteness

Claims 1-8 and 11-16 were rejected under Section 112, second paragraph, as being allegedly indefinite. Applicants traverse for the following reasons.

It was alleged that the recitation "originated from a wild type strain for production of an enzyme" in claim 1 is confusing. The mutants obtained by Applicants originated from a wild type strain, but they were obtained to be oxalate deficient and not to produce an enzyme. Applicants submit that the term "for production of an enzyme" is to be construed as "suitable for the production of an enzyme" (see claim 9). This claim construction is evident from the originally-filed disclosure at page 2, lines 21-24, and page 7, lines 12-14, of the specification wherein the term "suitable for" is explicitly used in the context of the subject matter of claim 1. To clarify this issue, claim 1 is amended to recite the term "suitable" to make the point explicit.

Further, it should be noted that *inter alia* the mutant strains obtained in Example 1 are oxalate deficient and do produce an enzyme (alpha amylase). This is clearly shown in Table 5 on pages 20-21 of the specification at page wherein 34 strains are listed as being oxalate deficient and producing alpha amylase. This emphasizes that the obtained strains are clearly suitable for the production of an enzyme.

Thus, Applicants submit that the claims are not confusing because the strains are suitable for production of an enzyme.

It was further alleged that the comparison between the mutants of WT2 and wild type WT1 that was not mutated (instead of mutated WT1) is confusing. In particular, claim 7 was rejected because "CBA 513.88 is not a proper control" and mutants of WT2 cannot be compared with wild type WT1 that does not possess amylase activity.

Due to the relationship between the WT1 and WT2 strains, the obtained mutant strains are mutated WT1 (CBS 513.88) strains. Therefore, the rational control to use is a non-mutated WT1 strain and consequently, proper controls were used with respect to the claimed subject matter. In the application as filed, the relationship between WT1 and WT2 is clearly set out. Their relationship is explained below.

In Experiment 1, it is described how WT2 cells (i.e., WT1 comprising copies of the alpha amylase gene) are mutated, mutants are selected for being oxalate negative, and the mutants produce at least the amount of enzyme (i.e., alpha amylase) as the wild type strain they originate from (WT2). Then in Experiment 2, it is described how from a selected mutant obtained in experiment 1 (mutant #22), the alpha amylase gene copies were deleted. The resulting strain was designated as FINAL. Thus, summarizing the strains and their relationship:

WT1 = CBS513.88

WT2 = WT1 + alpha amylase (i.e., CBS 513.88/alpha amylase)

Mutant = WT2 + UV mutagenesis (i.e., CBS 513.88/alpha amylase/UV mutagenesis)

FINAL = Mutant – alpha amylase (i.e., CBS 513.88/UV mutagenesis)

The claimed subject matter is: "An oxalate deficient *Aspergillus niger* mutant strain which originated from a wild type strain suitable for production of an enzyme, wherein said oxalate deficient strain produces at least the same amount of said enzyme

as the wild type strain produces under the same culture conditions." In the examples of the specification and the claims presented, the proper controls were used. Strain FINAL (Experiment 2) is a mutated WT1 strain. Thus, the rational control strain is non-mutated WT1.

In Examples 3 and 4 of the specification, endoprotease and phospholipase are expressed, respectively in strain FINAL. The proper control is the strain from which FINAL originates and expressing those enzymes: i.e., non-mutated WT1 transformed to express endoprotease and phospholipase.

In Example 1 of the specification, alpha amylase is expressed in WT1, the alpha amylase-expressing strain being designated WT2. After mutagenesis, mutants obtained from WT2 are, for the level of enzyme produced, compared to WT2 (i.e., non-mutated WT1 transformed to express alpha amylase).

Thus, Applicants submit that the claims are not confusing because the proper control is used to compare production levels of enzyme.

Finally, claims 13-16 are amended to indicate that they refer to "oxalate" levels. Basis for the amendment can be found in the specification at page 8, lines 7-9 and 22-24; and page 9, lines 17-20.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1-8 and 11-16 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. It was further alleged, "The claim(s) contains subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because their specification provides adequate written description for oxalate deficient *A. niger* strains.

Applicants submit that their claimed invention relates to oxalate deficient *A. niger* strains that produce at least the same amount of a desired enzyme as the parent strain. Thus, two characterizing features of the claimed strains are:

(i) oxalate deficiency and

(ii) production of at least the same amount of the desired enzyme as the wild type strain produces under the same culture conditions.

The claimed invention is not restricted to only one type of *A. niger* strain, but is applicable to all known *A. niger* strains. It should be noted, however, that the claimed invention is restricted to a single *Aspergillus* species, namely *Aspergillus niger*, a well-known producer of oxalate. Oxalate is, in turn, known to interfere with production of a desirable compound (see page 1, lines 8-10, of the specification).

No acceptable reasons were provided in the Office Action for a person skilled in the art to believe that the claimed invention would not be applicable to any *Aspergillus niger* strain. In contrast, the person skilled in the art is able to obtain the claimed strains without undue burden of experimentation using the teachings in Applicants' specification and the following available techniques:

- mutagenesis of a parent *A. niger* strain by any of the several methods known to the person skilled in the art (furthermore, a method is described in detail at page 10, lines 4-10, of the specification);
- determine whether an *A. niger* mutant strain is oxalate deficient with respect to the parent strain by use of the procedures set out in the examples (more specifically, Example 1); and
- determine the amount of enzyme in both the parent strain and the oxalate deficient strain for comparison, and whether the oxalate deficient strain produces at least the same amount of a desired enzyme as the parent strain by any of the several assays known to the person skilled in the art (furthermore, methods are

described in detail at page 3, lines 22-29, of the specification and such assays are shown in Examples 1-5 for alpha-amylase, phospholipases A1, and endo-protease).

As regards the objection to wild type strains and the use of proper controls for comparing amounts of enzyme produced, Applicants have explained the relationship between WT1 and WT2 in their rebuttal of the Section 112, second paragraph, rejection. As also explained therein, the proper controls for comparison have been used.

It was alleged on page 5 of the Office Action that "certainly there exists at least one enzyme in the whole metabolism of the mutant that is produced 'at least the same level' as in the wild type" but no evidence was provided to support this assumption. This assumption clearly does not apply to embodiments of the invention using an expression vector (see claims 4 and 5). It also does not apply to embodiments of the invention in which the amount of enzyme expressed is compared to expression in the reference strain CBS 513.88 (see claims 6 and 12). Even for other claims expressing a homologous enzyme without using an expression construct and comparing expression to the parent, wild type strain, there is no evidence that prior art *A. niger* mutant strains are suitable for production of enzyme in an industrial setting. As noted in the specification at page 1, lines 9-13, oxalate deficient *A. niger* mutant strains were not able to produce the enzyme at the level of the wild type strain they originated from under the same culture conditions. Thus, the prior art mutants were not suitable for producing polypeptide in an industrial setting.

In view of the reasons set forth above, Applicants submit that their specification and general knowledge in the art provide an adequate written description for the claims: i.e., the strains and methods required to practice their claimed invention in its full scope by assessing the two characterizing features of the claimed strains. A diverse variety of *Aspergillus niger* strains is known to the art. Using such wild type strains, the mutation and selection techniques taught by Applicants in their specification are sufficient to provide a representative number of the claimed mutant strains. Thus, the person skilled in the art is put in possession of the claimed invention.

Withdrawal of the written description rejection is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-2 were rejected under Section 102(b) as allegedly anticipated by Pedersen et al. (Metabol. Eng. 2:34-41, 2000). Applicants traverse.

Applicants' claims require that the oxalate deficient mutant strain produce at least the same amount of enzyme as its parent, wild type strain produces under the same culture conditions.

In contrast, Pedersen does not directly and unambiguously disclose an oxalate deficient *Aspergillus niger* strain that produces enzyme in at least the same amount as the parent strain. In this regard, it should be noted that the cited document was already distinguished in the specification at page 2, lines 8-14. Pedersen discloses a <u>decrease</u> in the amount of the enzyme glucoamylase produced by the oxalate deficient strain (see page 34, abstract, and page 39, left column, lines 11-14). Thus, the cited document teaches away from Applicants' invention. In fact, Pedersen indicates that a reasonable expectation of success was lacking in the prior art.

It was alleged on page 7 of the Office Action that synthesis of amino acids at a level not lower than in the wild type means that at least one of the enzymes involved in their synthesis was produced at a level not lower than in the wild type strain. This not an inference supported by the facts. As is well known in the art, the biosynthesis of amino acids involves multiple enzymes and, often, feedback regulation. The level of amino acid product does not directly and unambiguously indicate the amounts of the enzymes produced. For example, the stead state level of an amino acid may be increased by

altering its metabolism: enhancing amino acid synthesis, reducing use of amino acid in other biochemical pathways, or both.

Therefore, Pedersen does not anticipate claims 1-2.

Claims 4-5, 7-8 and 11 were rejected under Section 102(b) as allegedly anticipated by Hjort et al. (WO 00/50576). Applicants traverse.

Applicants' claims require the oxalate deficient strain to produce at least the same amount of enzyme as its parent, wild type strain produces under the same culture conditions.

In contrast, Hjort does not directly and unambiguously disclose an oxalate deficient *Aspergillus niger* strain that produces enzyme in at least the same amount as the parent strain. In this regard, it should be noted that the cited document was already distinguished in the specification at page 2, lines 1-8. Expression of heterologous polypeptides is described, but production of an enzyme such as amylase (note that alpha amylase is not disclosed in the cited document) is merely suggested (see pages 32-38). No expression construct comprising a gene encoding an enzyme was actually used in Hjort. And there is no indication whatsoever of the amount of any enzyme which might be produced by the oxalate deficient strain.

Therefore, Hjort does not anticipate claims 4-5, 7-8 and 11.

Applicants submit that this feature of their claimed invention (i.e., the oxalate deficient *Aspergillus niger* mutant strain produces enzyme in at least the same amount as the parent, wild type strain) is sufficient to distinguish over the cited documents so any other incorrect allegations about the disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 102 rejections is requested because the Pedersen and Hjort documents fail to disclose all limitations of the claimed invention.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100